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Effect of 4-prothrombin complex concentrate on mortality in patients presenting to the emergency department with warfarin-induced bleeding

4-prothrombin complex concentrate roll in warfarin induced bleeding

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Abstract
Aim: Today, it has been observed that the increase in the use of vitamin K antagonists (VKA) causes various complications, from acute bleeding to death. Fresh frozen plasma and 4-prothrombin complex concentrate (4-PCC) are still used in the treatment of these patients. In our study, we aimed to investigate the effect of 4-PCC use on early mortality in patients presenting with bleeding due to VKA.
Material and Methods: Our study was conducted in a district state hospital with a retrospective and single-center design. It enrolled a total of 89 patients with a history of vitamin K antagonist drug use; patients with a history of trauma-induced hemorrhage or hematological disease were excluded.
Results: Out of 89 patients with a mean age of 71.00±10.79 years, 51.7% were male and 51.7% had a major hemorrhage and 48.3% had minor hemorrhage. Twenty-seven percent of the patients died despite treatment. The mean post-admission INR level was 9.48±5.8. Post-treatment and 24-hour INR levels were significantly lower in both patient groups treated with 4-PCC and FFP. It was determined that the administration of vitamin K did not lead to any significant difference in both patient groups treated with FFP and 4-PCC. Additionally, the treatment lasted 4 times longer, and the mortality rate was 4 times higher among patients treated with FFP than those treated with 4-PCC.
Discussion: We detected that the use of 4-PCC to reverse the anticoagulant effect will provide more rapid treatment, less volume loading, and lower mortality among patients using VKAs.

Keywords
Hemorrhage; Vitamin K Antagonist; Prothrombin Complex Concentrate

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Introduction

Vitamin K antagonists (VKAs) are currently among widely prescribed medications. Many studies in the literature have reported that these agents effectively treat and prevent many thromboembolic events [1]. However, these agents have a narrow therapeutic range, which may cause complications [2,3]. These complications include major hemorrhages such as intracranial hemorrhage and gastrointestinal hemorrhage and minor hemorrhages such as epistaxis, gingival bleeding, and hematuria [4,5]. The risk of hemorrhage particularly increases when the international normalized ratio (INR) level rises above 5.0 [5]. Therefore, patients using these agents frequently present to the emergency department with hemorrhage [6].

There are times when rapid intervention is required in patients who present to the emergency department with VKA-induced hemorrhage. In some of these conditions, such as intracranial bleeding requiring surgery or massive gastrointestinal bleeding requiring interventional procedures, it may be necessary to reverse the effect of CVA [7]. Although vitamin K administration is part of the routine procedure in such patients, it may take up to 4 hours in intravenous administration and 24 hours in oral administration for INR starting to fall [8-10].

Currently, fresh frozen plasma (FFP) is widely used to reverse the effects of VKAs. However, FFP has some disadvantages such as long preparation time, risk of transfusion reactions, and volume loading [11,12].

Four-prothrombin complex concentrate (4-PCC) contains factor 7 in addition to vitamin K-dependent coagulation factors 2, 9, and 10 [11,13]. Whereas normalizing INR with FFP is often difficult and takes a long time, 4-PPC fulfills this task quickly and effectively [11,14]. 4-PPC has been used to reverse the effect of VKAs for a long time now. International guidelines also recommended the use of 4-PPC for an urgent reversal of INR in VKA-induced hemorrhage [15].

In this study, we aimed to investigate the effect of the use of 4-PCC on early mortality among patients presenting with VKA-induced hemorrhage.

Material and Methods

Study Design

Our study retrospectively recorded the medical data of successive patients older than 18 years of age who presented to the emergency department with VKA-induced hemorrhage. The study participants were those who were known to be previously administered VKA agents against thromboembolic events. Early in-hospital mortality was recorded from patient records during the hospital stay.

Study Settings and Population

This study was designed to be conducted between January 1, 2018, and January 1, 2020, in the emergency department of a district state hospital with a capacity of approximately 500 emergencies per day and 150 beds. The study population was composed of patients older than 18 years with complete medical records, who presented to the emergency with VKA-induced hemorrhage. A hemorrhage was detected by an emergency medicine specialist.

Our study design excluded patients with traumatic hemorrhage, a history of the hematological disease, and an unclear history of VKA use.

Patient records were obtained from the hospital automation system and medical records archive. In-hospital mortality was defined as death occurring within 7 days after hospital admission.

Study Protocol

Before the collection of the patients' data, an ethics committee approval was obtained (ethics committee no. E-37201737-806.02.02). Patients using VKA who presented to the emergency department with acute hemorrhage were retrospectively identified with the help of the hospital data management system. Their age, sex, indications for VKA use, and outcomes were recorded from the hospital data management system. The same system was also used to record the treatments administered to the patients (vitamin K, fresh frozen plasma (10mL/kg), and 4-PCC (50 IU/kg)) and their duration of administration, patient outcomes (admission to a regular ward, admission to intensive care unit, or discharge), and mortality data. All data were recorded on previously prepared study forms.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 20.0 software was used for the statistical analysis of all the data obtained. All data were summarized in tables during evaluation. The Mann-Whitney U test was used to compare the mean values of the data obtained, and the Pearson Chi-Square (and the Fisher's exact test when required) was used to compare non-parametric data.

The results were considered significant at $p<0.05$, with a 95% confidence interval.

Results

Our study included 89 patients, of whom 43 (48.3%) were female and 46 (51.7%) were male. The mean age of the study population was 71.00±10.79 years. The indications for VKA use was a history of atrial fibrillation (AF) in 29.2% of the patients, valve replacement in 40.4%, cerebrovascular disease (CVD) in 10.1%, pulmonary thromboembolism (PTE) in 4.5%, deep vein thrombosis (DVT) in 6.7%, and other causes in 9%. Forty-five (51.7%) patients were found to have major hemorrhage and 44 (48.3%) had minor hemorrhage at emergency department admission. Among patients with major hemorrhage, 21 (46.6%) had intracranial hemorrhage, 20 (44.4%) had gastrointestinal system (GIS) hemorrhage, and 4 (8.9%) had a pericardial hemorrhage. Minor hemorrhage included hematuria in 18 (40.9%) patients and gingival hemorrhage in 26 (59.1%). Twenty-five percent of the patients died despite treatment (Table 1).

After admission, patients were evaluated, their laboratory tests were ordered, and treatment was started. The mean INR on admission was 9.48±5.8 (Table 1). VKA-induced bleeding was treated with 4-PCC (50 IU/kg) in 38.2% of patients and FPP in 61.8%. Vitamin K was administered to 44.9% of patients, but not to 55.1% of them. Patients treated with 4-PCC had a mean pre-treatment INR level of 8.68±5.51, a mean immediate post-treatment INR level of 1.91±0.93, and a mean 24th hour INR level of 2.44±1.31. Patients treated with FFP had a mean pre-treatment INR level of 9.98±5.96, a mean immediate

Table 1. Analysis of demographic and historical data of the study population

Parameter	n (%)/ Mean±SD	p
Number of cases	89 (100)	
Age (years)	71.00±10.79	
Gender		
Male	46 (51.7)	
Female	43 (48.3)	
Indication for VKA use		
Valve replacement	36 (40.4)	
AF	26 (29.2)	
CVA	9 (10.1)	
PTE	4 (4.5)	
DVT	6 (6.7)	
Other	8 (9.0)	
Admission INR level	9.48±5.8	
Major bleeding	45 (51.7)	
Intracranial Bleeding	21 (46.6)	
GIS Bleeding	20 (44.4)	
Pericardial Bleeding	4 (8.9)	
Minor bleeding	44 (48.3)	
Gingival bleeding	26 (59.1)	
Hematuria	18 (40.9)	
Outcome		
Survived	64 (71.9)	
Mortality	25 (28.1)	
Post-FFP treatment		
Survived	35 (63.6)	0.031*
Mortality	20 (36.4)	
Post-4-PCC Treatment		
Survived	29 (85.6)	
Mortality	5 (14.4)	
Mean duration of treatment (min)		
FFP	118.24±43.2	<0.001**
4-PCC	31.18±7.46	

*: Pearson Chi-square Test
**: Independent samples T-Test

post-treatment INR level of 3.03±1.53, and a mean 24th hour INR level of 2.88±2.10. An analysis of the change in INR levels showed that patients treated with FFP (10 mL/kg) had significantly lower post-treatment INR than the admission INR. Similarly, patients treated with 4-PCC also had a significantly lower post-treatment INR level than the admission INR. However, the analysis of the 24th hour INR levels showed a significant rise in the INR level in the 4-PCC group but not in the FFP group (Table 2).

An analysis of INR levels by the status of treatment with vitamin K showed a mean post-treatment INR level of 1.82±0.35 and a mean 24th hour INR level of 2.33 ±0.44 in patients treated both with vitamin K and FFP, and a mean post-treatment INR level of 1.20±0.22 and a mean 24th hour INR level of 1.87 ±0.35 in patients treated with FFP alone. Among patients treated with FFP, the mean post-treatment INR level and the mean 24th hour INR level showed no significant difference from the mean admission INR level with respect to the treatment with vitamin K (Table 3). An analysis of the INR levels by the status of treatment with vitamin K showed a mean post-treatment

Table 2. Comparison of the admission, post-treatment, and 24th hour INR levels between the TDP-administered and the 4-PCC-administered groups.

Administered Treatment	n (%)	Admission INR Mean±SD	Post-treatment INR Mean±SD	24th hour INR Mean±SD	p1	p2	p3
FFP	55	9.98±5.96	3.03±1.53	2.88±2.10	<0.001	<0.001	597
4-PCC	34	8.68±5.51	1.91±0.93	2.44±1.31	<0.001	<0.001	37

p1: Admission INR & Post-treatment INR; p2: Admission INR & 24th hour INR; p3: Post-treatment INR & 24th hour INR; Paired T-Test was used.

Table 3. Comparison of the admission, post-treatment, and 24th hour INR levels of patients treated with FFP and 4-PCC by the status of treatment with vitamin K treatment

Administered Treatment	n (%)	Admission INR Mean±SD	Post-treatment INR Mean±SD	24th hour INR Mean±SD	p1	p2
Vitamin K + FFP	27	9.98±5.96	3.10±1.82	2.72±2.33	751	562
FFP	28		2.97±1.0	3.05±1.87		
vitamin K + 4-PCC	13	8.68±5.51	1.87±0.83	2.31±1.10	860	642
4-PCC	21		1.93±1.01	2.53±1.44		

p1: Comparison with the mean post-treatment INR; p2: Comparison with the mean 24th hour INR;
Independent samples T-Test was used.

INR level of 1.87±0.83 and a mean 24th hour INR level of 2.31 ±1.10 in patients treated with both vitamin K and 4-PCC, and a mean post-treatment INR level of 6.41±1.39 and a mean 24th hour INR level of 2.53 ±1.44 in patients treated with 4-PCC alone. Among patients treated with 4-PCC, the mean post-treatment INR level and the mean 24th hour INR level showed no significant difference from the mean admission INR level by the status of treatment with vitamin K (Table 3).

Comparison of post-treatment mortality rates showed a mortality rate of 36.4% among patients treated with FFP and only 14.4% in patients treated with 4-PCC, with the difference being statistically significant (p=0.031) (Table 1). In addition, comparison of the duration of administration revealed a significant difference between the 4-PCC treatment and the FFP treatment (Table 1).

Discussion

Warfarin is the most widely used VKA drug. It acts by preventing the synthesis of vitamin K-dependent coagulation factors (factor 2, 7, 9, 10), with effective anticoagulation being determined by the therapeutic INR range [16]. 4-PCC and FFP are among the current treatments for the reversal VKAs' effects in patients presenting with acute hemorrhage. Our study showed that 4-PCC reduced admission INR level to lower post-treatment levels compared with FFP among patients using VKAs and presenting with acute hemorrhage. Demeyere et al. reported that 4-PCC provided a quicker and more effective reversal of VKAs' effects compared with FFP in patients with a history of cardiopulmonary bypass [17]. Similarly, Hickey et al. detected that 4-PCC reversed the effect of VKAs more quickly and more effectively than FFP in the emergency department [18]. In addition to the treatment efficacy, the duration of the treatment also guides the clinician in the choice of treatment in patients with acute hemorrhage. Due to the need for blood

group determination and longer preparation and infusion times, it is very unlikely for FFP to have a shorter duration of administration than 4-PCC. Hence, our study demonstrated a significantly shorter time to start 4-PCC treatment than FFP. Similarly, there is a consensus among prior studies in the literature that 4-PCC is associated with a shorter time to start treatment [19, 20]. Our findings support the literature data.

Our study demonstrated that administering vitamin K did not cause any significant difference in INR reversal in patients treated with FFP or 4-PPC. In addition, we did not find any significant difference regarding whether the administration of vitamin K was a cause of rebound INR elevation in both FFP and 4-PCC groups. Comparison of the study groups in terms of volume overloading showed that FFP caused a greater volume load compared with 4-PCC. Therefore, we believe that 4-PCC would be beneficial in terms of volume overload. Our study found a mortality rate of 28.1% in our study population; of those who died, 20 patients were treated with FFP, and the remaining 5 with 4-PCC. Comparison of the mortality rates in both groups showed that the mortality rate was significantly lower in the 4-PCC group. We suggest that more rapid administration and less volume overload with 4-PCC caused this difference in mortality rates. In a nationwide study, Zeeshan et al. found that 4-PCC significantly increased survival among trauma victims [21].

Limitations

Our study has some limitations. Firstly, it was inevitable to have some missing data due to the retrospective nature of the study. Patients lost to follow-up may have died in other hospitals. Secondly, this was a single-center study, and thus our sample size was small. Lastly, physiological vital signs could not be used due to incomplete records at the time of admission.

Conclusion

We concluded that the use of 4-PCC to reverse the anticoagulant effect among patients using VKAs will ensure a more rapid treatment, cause less volume overloading, and result in a lower mortality rate. We believe that FFP may be life-saving when 4-PCC is unavailable or contraindicated; otherwise, 4-PCC should be kept in mind as the first option for the treatment of patients with acute hemorrhage.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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